

# Anticoagulant Treatment in Coronary Heart Disease

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The anticoagulant treatment of coronary disease in general and myocardial infarction in particular has received world-wide appraisal following its inception 25 years ago. After an initially enthusiastic reception it began to lose favour. In the light of recent publications it appears appropriate to consider further a previously reported series of cases that has now been followed up for a further three years.

## SUBJECTS AND METHODS

A series of 461 cases of coronary disease, treated with anticoagulants, was reported in 1966 and 1967 (Royston, 1966, 1967). The cases were drawn from a typically suburban dormitory area with a small industrial population and treated under the National Health Service. The cases were divided into two groups: those with myocardial infarction with or without previous angina, and those with angina without any history to suggest a previous frank myocardial infarct. The myocardial infarction cases were subdivided into the age-groups of under 55 years and 55 years and over. Deaths in hospital, anticoagulant treatment for less than 1 month, a history of peptic ulcer, gross obesity, and a blood pressure over 110 mm. Hg diastolic led to exclusion.

All patients were traced successfully, and, when alive and unable to attend for a personal interview, they were considered as withdrawals at the time of their last attendance reported in the case papers.

Details of deaths were obtained from hospital records, general practitioners, coroners' officers, and post-mortem records.

The survivors from the original series have been followed up for a further 550 treatment years to a total of 1700 treatment years. The duration of treatment is illustrated in Fig. 1 and the age distribution at the onset of treatment in Fig. 2.

Treatment was stopped in 31 patients: 8 for haemorrhage (2 with underlying pathological lesions), 14 for neoplasms, operations, or irregular attendance, and 9 for change of domicile. They were all treated as withdrawals from the trial on stopping anticoagulant treatment.

The calculation of results included all patients admitted to the trial whether withdrawn or not. Where anticoagulant treatment was stopped for a condition from which death followed or death occurred within

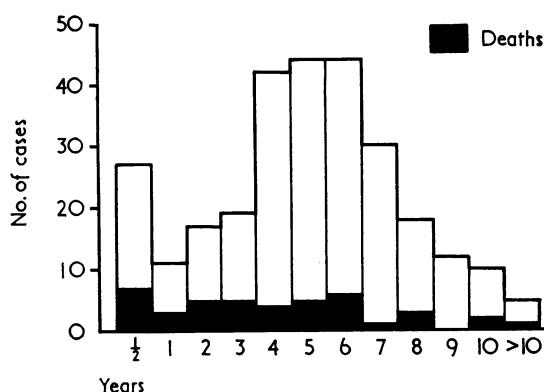


FIG. 1.—Duration of anticoagulant treatment.

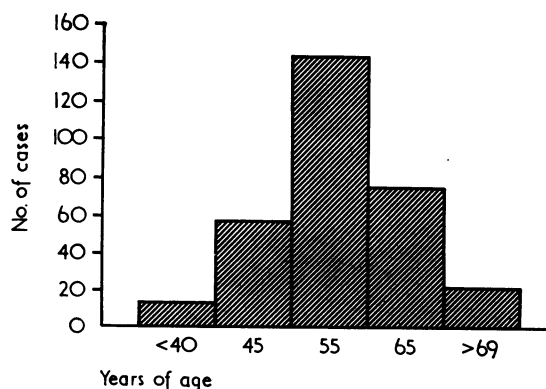


FIG. 2.—Age distribution for all cases of myocardial infarction with and without a history of previous angina.

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TABLE I

SURVIVAL RATE FOR ALL MEN ON ANTICOAGULANTS FOLLOWING MYOCARDIAL INFARCTION WITH OR WITHOUT PREVIOUS MYOCARDIAL INFARCTION AND OR ANGINA

Months on treatment	No. of cases	Withdrawals	Deaths	Per cent survival to end of interval
0- 6	279	22	7	97.4
7- 12	250	12	3	96.2
13- 24	235	10	6	93.7
25- 36	219	16	5	91.5
37- 48	198	31	7	88.0
49- 60	160	41	9	82.3
61- 72	110	34	2	80.5
73- 84	74	29	1	79.2
85- 96	44	14	3	72.7
97-108	27	12	2	65.8
109-120	13	8	0	65.8

one month, this death was considered to have occurred while on treatment. There was no death from re-infarction within one month of stopping anticoagulant treatment.

#### RESULTS

**Myocardial Infarction.** The survival rate for 279 men of all ages after myocardial infarction, including those with a previous history of infarction or angina, is 91.5 per cent at three years, 82 per cent at five years, 79 per cent at seven years, and 66 per cent at ten years (Table I and Fig. 3). Comparing the age-groups of under 55, and of 55 and over, the three- and five-year survival rates show the ex-

TABLE II

MEN ON ANTICOAGULANTS WITH MYOCARDIAL INFARCTION WITH AND WITHOUT PREVIOUS ANGINA AND OR MYOCARDIAL INFARCTION

Months	Age (yr.)	No. of cases	Withdrawals	Deaths Total	Per cent survival at end of interval
0- 6	<55	126	12	1	99.2
	≥55	153	10	6	96.0
7- 12	<55	113	3	1	98.3
	≥55	137	9	2	94.5
13- 24	<55	109	2	1	97.4
	≥55	126	8	5	90.6
25- 36	<55	106	10	0	97.4
	≥55	113	6	5	86.5
37- 48	<55	96	13	2	95.2
	≥55	102	18	5	81.9
49- 60	<55	81	16	3	91.3
	≥55	79	25	6	74.5
61- 84	<55	62	37	2	87.1
	≥55	48	26	1	72.4
85-120	<55	23	19	3	67.7
	≥55	21	16	2	61.2

pected differences favouring the younger group, i.e. 97 and 91 per cent, as opposed to 86.5 and 74.5 per cent (Table II).

In terms of man months the mortality is 0.25/100 man months compared with the earlier figure of 0.33/100 man months (Royston, 1967).

**Angina.** The 108 cases of angina of all ages without any history of myocardial infarction have a 3- and 5-year survival rate of 93 and 83 per cent, respectively, and 72 per cent at 7 years (Table III, Fig. 4).

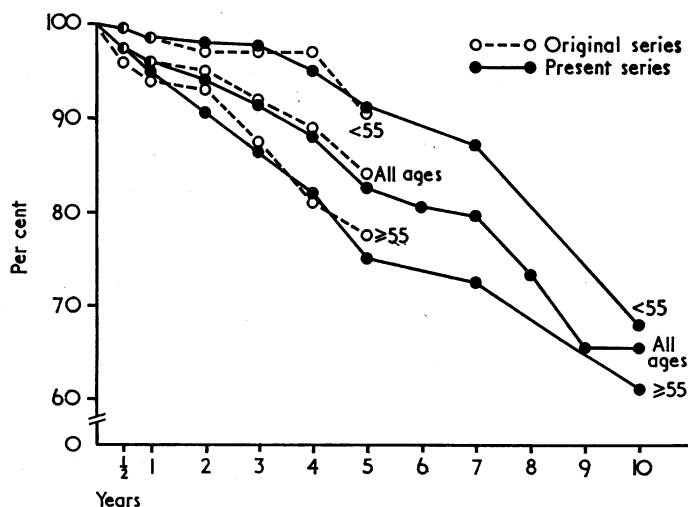


FIG. 3.—Survival following myocardial infarction treated with anticoagulant treatment.

TABLE III

## ANGINA WITHOUT MYOCARDIAL INFARCTION

Months	No. of cases	Withdrawals	Deaths	Per cent survival to end of interval
0-6	108	2	4	96.3
7-12	102	6	2	94.3
13-24	94	7	1	93.3
25-36	86	6	0	93.3
37-48	80	14	2	90.7
49-60	64	10	5	83.1
61-72	49	25	0	83.1
73-84	24	4	3	71.8

## DISCUSSION

In the original series the results after 1150 treatment years of anticoagulant treatment were shown to compare favourably with other published series of both treated and untreated patients (Royston, 1967). It was suggested that the good results were largely due to the high level of anticoagulation obtained for 80 per cent of the treatment time, and it was concluded that long-term anticoagulant treatment was indicated in coronary disease. From Fig. 3 it can be seen that the further period of observation of 550 treatment years has confirmed the earlier findings, there being no significant change in the survival pattern, either for all the cases taken together or for the two age-groups separately. After myocardial infarction the survival rates of 91.5, 82, 79, and 66 per cent at 3, 5, 7, and 10 years, respectively, are similar to 91 and 83 per cent at 3 and 5 years, as originally described (Table I and Fig. 3). The mortality of 0.25/100 man months is an improvement on the original figure of 0.33/100

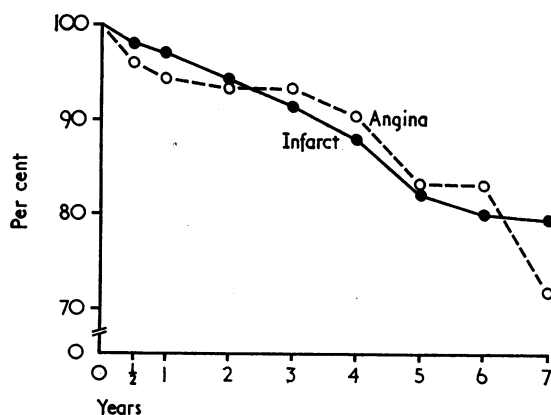


FIG. 4.—Angina and myocardial infarction, survival on anticoagulant treatment.

man months over the shorter term, and having been arrived at over a longer period of observation, it is more significant. It compares favourably with the low dosage group in the Medical Research Council trial (A Research Committee, 1965) which can be considered to be inadequately treated, where the mortality was 0.80 per 100 man months.

Recently, Lovell *et al.* (1967) have recorded a survival rate for men of all ages on anticoagulant treatment of about 90 per cent at 1 year, 85 per cent at 2 years, and 75 per cent at 3 years, though the latter figure related to a small number of cases. In the present series, the survival rate at one year is 96 per cent and at 2 years 95 per cent, and falls from 91.5 to 82 per cent over the three-five-year period, the number of cases observed being 160 at 5 years. These figures endorse Lovell's findings, and owing to the greater number treated at 3 years, are more significant at that level.

Lovell felt that anticoagulant treatment improved the prognosis only in his patients aged 55 years and under. Table II and Fig. 3 show that, in the present series, though the younger age-group does better than the older, the benefit is not confined to it, nor is the benefit only confined to the first two years of treatment. In another controlled trial (Report of the U.S. Veterans Administration, 1965) there were 476 men, aged 55 and under: in the group on anticoagulants the survival rates at two years and three years were 94 and 90 per cent, compared with 97 and 86.5 per cent for this series.

In 1965 in the M.R.C. low fat trial (A Research Committee, 1965) 252 men with recent myocardial infarction under the age of 60 and without a previous infarct were treated without long-term anticoagulants. They were drawn from a similar population to the present series, were treated in similar hospitals, and the same criteria for diagnosis were used. They therefore form a reasonable control group, though not a perfect one. Any bias is against the present series which contains over 30 per cent of men aged over 59, a proportion of second infarcts and associated medical conditions, all those that would have been excluded from the M.R.C. trial. The M.R.C. reported survival at 3 years and 5 years of 84.7 and 77.2 per cent compared with 91.5 and 82 per cent (Fig. 5). The present series is significantly better at both intervals:  $p = <0.01$  and  $<0.0005$ , respectively.

C. F. Borchgrevink (*World Med.*, 1967), speaking at the Lauder Brunton Centenary Symposium in Edinburgh last year, reported a 5-year survival of 93 per cent in angina on anticoagulant treatment against a control figure of 70 per cent. These are the best figures reported so far. He contends that anticoagulant treatment is of value in angina. The

present results support this view, being significantly better than his control figures.

Considering all cases of coronary disease with or without infarction, a comparison between the outlook for angina alone and those with infarcts shows great similarity, provided they are both receiving anticoagulant treatment (Fig. 4). The infarction group represents the survivors after admission to hospital, and can be expected already to have suffered about a 20 per cent mortality in hospital. Even a special coronary unit has recently had a mortality of 17.5 per cent (Lawrie *et al.*, 1967).

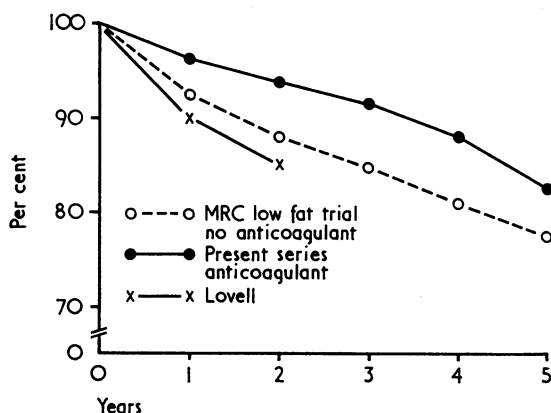


FIG. 5.—Survival after myocardial infarction.

When this initial mortality is taken into consideration, it appears that for every 100 patients admitted with infarction there will be 80 survivors, and these will experience a further mortality of 18 at 5 years, yielding a final 5-year figure of 66 per cent. This compares unfavourably with 83 per cent for angina treated before infarction has occurred. It seems that in hospital cases, provided recovery occurs from the initial infarct, and long-term anticoagulant treatment is given, the episode of infarction has surprisingly little effect on the long-term prognosis, as compared with coronary disease manifested by angina alone similarly treated. It therefore seems wise to instigate anticoagulant treatment as soon as the diagnosis of angina is made rather than wait for infarction to occur with its additional mortality in hospital.

Further study is required to determine the optimum period of treatment and the age limit above which anticoagulant treatment would not normally be started. Consideration must also be given as to whether anticoagulant treatment already begun

should be continued beyond this limit or withdrawn.

Though there were no controls within this trial, the results are worthy of consideration. They show the outcome of anticoagulant treatment in a suburban area of London under the National Health Service. Before these results are ignored simply on the grounds of the lack of controls, similar or better results should be reported under approximately similar conditions, where the patients are not receiving anticoagulants. This so far has not been done.

In view of the previous results (Royston, 1966, 1967), it was felt that it was unethical to deny anticoagulant treatment to suitable cases. The further observation of the original series confirms this view.

### CONCLUSIONS

Studies have been made on 461 cases of coronary disease previously reported and treated with anticoagulants for a further 550 treatment years, making a total of 1700.

The survival rates for myocardial infarction among patients on anticoagulant treatment after discharge from hospital were at all ages, 91.5 per cent at 3 years and 82 per cent at 5 years, or 0.25 deaths per 100 man-months.

The under 55 age-group fared better than the older group, being 97.4 and 91.3 per cent at 3 and 5 years, compared with 86.5 and 74.5 per cent, respectively.

The survival rates in angina for all ages on anticoagulant treatment were 93 per cent at 3 years and 83 per cent at 5 years.

With long-term anticoagulation, survivors from myocardial infarction have the same survival rate over 5 years as cases of angina without infarction similarly treated.

Anticoagulant therapy is the long-term treatment of choice in men with coronary heart disease, whether manifested by angina alone or by frank myocardial infarction. Such treatment should be continued for at least 5 years and probably longer. Further study is required to determine its optimum duration.

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